UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/664,225	09/18/2000	Mary Lynne Hedley	08191/013001	4277

26161 7590 01/16/2003

FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/16/2003

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/664,225	Hedley
Examiner	**Art Unit**
Dave Nguyen	1632

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 4, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-44, 46-66, 68, and 69* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *1-44, 46-59, 68, and 69* is/are allowed.

6) ☒ Claim(s) *60-62* is/are rejected.

7) ☒ Claim(s) *63-66* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 8
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claims 45, 67 have been canceled, claims 1, 5, 47 and 52 have been amended by the amendment filed November 4, 2002.

The species restriction has been vacated by the examiner because the prior art rejection of record has been withdrawn by the examiner, and because the prior art of record does not teach or suggest the claimed invention, particularly wherein a DNA construct encoding a hybrid polypeptide comprising a target signal sequence and polyepitopes of naturally occurring pathogenic proteins, wherein the epitopes are either contiguous or are separated by a spacer amino acid or spacer peptide.

Elected claims 1-44, 46-66, 68 and 69, drawn to a hybrid DNA encoding multiple epitope(s) of viral antigens, method of virally infected treatment by DNA applications, to which the following grounds of rejection remain applicable, are pending for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 60-62, readable on an immunization method of any polyepitope encoded DNA vaccine or immunogenic composition to a virally infected human patient or a human at risk of a viral infection, remain rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims recite a generic claimed invention as recited in the base claim 60. The specification does not reasonably provide enablement for any other claimed embodiment, wherein any non-route of administration is employed so as to target any tissue site containing any antigen presenting cell in a human subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, particularly when the claims recite

---

specifically that the claimed DNA immunogenic composition in any polyepitope form can be used

without any undue experimentation so as to induce a beneficial and/or protective immune response in the human subject as contemplated by the as-filed specification.

With respect to methods of expressing MHC class I or MHC class II binding epitopes at any target site of any human patient or subject within the context of the claimed invention, wherein any administration route is embraced, the specification does not provide sufficient guidance and/or evidences for one skilled in the art to reasonably extrapolate, without undue experimentation, from a simple murine model of transgenic HLA-A *0201/H2Kb mice showing CTL responses generated as a result of intramuscular injection of microspheres encapsulating DNA encoding a polyepitope HPV polypeptide to any other claimed embodiment as embraced by the breadth of claimed invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention which contemplates that any of the disclosed DNA constructs would exhibit a therapeutically immune effect in any mammal including a human (see claim 61) when administered using any route of administration in a human subject. The state of the art exemplified by McCluskie *et al.* (Molecular Medicine, 5, pp. 287-300, 1999) indicates:

- "The route of deliver of the DNA vaccine can have an impact on the efficiency of transfection as well as the types and location of cells transfected, and thu8s potentially on the nature of the immune response" (page 295, column 1 bridging column 2);
- "More recent with antigen-encoding plasmids have shown that antigen expression does not continue indefinitely, but rather is lost by some immune-mediated mechanism around 2-3 weeks after DNA injection" (page 295, column 2, last paragraph); and

- A number of factors appear to influence the Th bias of the immune response, including (i) the angigen; (ii) the dose of antigen; (iii) whether the antigen is secreted, cytoplasmic, or membrane bound; (iv) the route and method of DNA administration; (v) the number of immunizations; (vi) the presence of CpG motifs; (vii) the haplotype of the mouse immunized; (viii) the presence of adjuvant; (ix) co-expression of cytokines; (x) whether DNA is formulated (e.g., with cationic liposomes); and (xi) rest period between immunizations (page 296, column 1).

Even if an animal model including a mouse model may show a desire immune response (CTL responses) by art-recognized intramuscular injection route, McCluskie *et al.* teach that "the realization that results in mice often do not predict the situation in humans has also led to a large number of DNA vaccine studies in nun-human primates", that "IM injection of plasmid DNA vaccines, while highly immunogenic in mice...was found to be only relatively so in chimpanzees..., and especially not all in Aotus monkeys", and that "it is probably safe to say that any vaccine that works in a human [emphasis added] will work in a mouse, but not necessarily vice versa" (page 296, column 2, second and third paragraphs). In addition and as to mucosal routes as embraced by the claims, McCluskie *et al.* teach that "the generally absent responses with the noninjected routes were not unexpected, as the mucosal surfaces are protective barriers, physiologically designed to limit uptake of bacteria, viruses, antigens" (page 296, column 1), and that "although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predictive they will be in the case of DNA vaccines where efficacy, by virtue of the requirement first to transfect cells and express the antigen, relies on many factors other than immunological responses to the antigen" (page 297, column 1).

In view of the reasonable unpredictability of the state of the art of DNA immunization methods as indicated in the exemplified McCluskie *et al.* reference, one skilled in the art then turns this instant specification for guidance, however, other than simple CTL responses generated in transgenic mice which is not even a real-world mammal intended for the contemplated utility, as the result an intramuscular injection of microspheres encapsulating

---

plasmid vectors encoding HPV epitopes, the specification does not provide sufficient guidance

and/or evidence to overcome the obstacles as disclosed in the state of the prior art.

Even if a partially protective and/or therapeutic response has been shown in mice using the exemplified protocol, it is not apparent as to how the murine model using one single species of HPV encoded plasmid encapsulated in microspheres is reasonably extrapolated to the full scope of the claimed invention including a human subject at risk or being infected by any pathogenic pathogen, particularly given that there is no evidence that the murine model is a general phenomenon for any other claimed embodiment, and given the doubts expressed in the art of record.

Furthermore and with respect to vaccination and/or therapy methods encompassing non-injection routes, *e.g.,* inhalation and oral administration, the state of the art exemplified by Cryz *et al.* (Vaccine, Vol. 14, 7, Vaccine Delivery Systems, Reports of the Expert Panels, pages 665-688) indicates that oral delivery of any vaccine to gastrointestinal cells, *e.g.,* M cells, so as to have a therapeutic effect, remains unpredictable at the time the invention was made (page 674, columns 1 and 2). More specifically, Cryz *et al.* teach:

"Effective delivery to the GALT [gastrointestinal associated lymphoid tissue] is predicated with enormous problems. While it is a relatively simple task to deliver particles to certain sites in the intestine, the efficiency of uptake is very low. Recent studies suggest that less than a fraction of one percent of particles are taken up and translocated. Indeed recent studies in the UK failed to demonstrate the presence of fluorescent particles in M-cells of human subjects after repeated dosing with particulate carriers. Attempts have been made to improve the efficiency of the process by the use of particles carrying appropriate monoclonal antibodies or lectins but the results are not especially encouraging. The use of lipid vehicles could have some advantages. Not surprisingly, the gastrointestinal tract, because of its very nature, will be a less efficient site for particle uptake than other mucosal surfaces. The process of presentation of a particle to M-cells is obviously a statistical problem. How does a particle in the centre of the lumen, carrying a receptor for M-cell interaction, 'know' that there are M-cells in the vicinity?" (page 674, column 2).

Thus, it is not apparent how one skilled in the art, without undue experimentation, practices the full scope of the claimed invention, and/or uses the DNA immunization methods as

claimed to provide an active immunity for any future protection and/or therapeutic efficacy against an infection by any and/or strains of a pathogenic organism, particularly on the basis of applicant's disclosure, and in view of the doubts expressed in the art of record at the time the invention was made.

Applicant's response (filed November 4, 2002, pages 4-6) has been considered by the examiner but is not found persuasive for the reasons of record and for the following reasons:

Without providing any evidentiary support so as to overcome the doubts expressed by the art of record, Applicant assert that sufficient guidance regarding routes of administration and types of carriers are well described by the as-filed specification and prior art of record. However and notwithstanding the fact that skill of a person skilled in the art of DNA vaccine is relatively high, that fact the prior art of record have actively involved in further experimentation of finding out solutions and/or particular types of carriers so as to overcome the barriers and/or the lack of reasonable predictability in practicing any DNA vaccine in human subjects as claimed. The only novel contribution on the basis of the as-filed specification is the concept of employing a polyepitope encoded DNA construct in a DNA vaccination method, however, neither the as-filed specification provide any solution so as to overcome the doubts expressed by the art of record in performing any DNA vaccine and/or therapeutically immunogenic composition in any human patient as broadly claimed, nor does the as-filed specification provide any guidance and/or factual evidence as to how to lead one skill in the art, without any undue experimentation, to determine as to which carriers and/or microsphere/microparticle from the prior art would be prophylactically and/or therapeutically effective within applicant's context of the claimed invention, nor does the as-filed specification provide any guidance so as to reasonably extrapolate from a simple murine model to an efficacy in any human subject as generically claimed, particularly in view of the requirement of the *Wands* factors which has not been sufficiently met by the as-filed specification, and in view of the totality of the art of record regarding the state of the DNA vaccine art and/or therapeutically immunogenic DNA composition in human subjects.

Note also that the court decisions cited in In re Wright, (CA FC) 27 USPQ2d

1510 (1993), Enzo Biochem Inc. v. Calgene Inc., 188F .3d 1362, 1374, 52 USPW2d 1129, 1138 (Fed. Cir. 1999). See also Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997):

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a genetic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable of the public to understand and carry out the invention.").

In addition and as analogously explained in In re Wright, (CA FC) 27 USPQ2d 1510 (1993), the claims are directed to methods of using DNA vaccines in a human at risk of being infected by any viral infection including an HPV infection, which must by definition trigger a therapeutic or an immunoprotective response in the vaccinated or immunized human; mere antigenic response or a simple detection of an transient antibody response is not enough. In addition, Appellants attempt to claim in the claims of *any* DNA vaccineencoding *any* HPE polyepitope. In fact, in Wright's case, the court decision states:

"[M]many of the appealed claims encompass vaccines against AIDS viruses and that, because of the high degree of genetic, antigenic variations in such viruses, no one has yet [even in 1993 when the court decision was made], years after his invention, developed a generally successful AIDS virus vaccine" (page 1513);

The following references are further cited to indicate that lack of reasonable predictability of DNA vaccine in human subjects:

Richardson, Journal of General Virology, 83:2515-2521, 2002.

Claims 1-44, 46-59, 68 and 69 are in condition for allowance.

Claims 63-66 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER